[CLEAN FORM OF PARAGRAPH 9]

[009] Some years ago, a further method of DNA sequencing was developed on the basis of optical (or autoradiographical) detection, namely sequencing by oligomer hybridization (cf. e.g. Drmanac et al., Genomics 4, (1989), pp. 114-128 or Bains et al., Theor. Biol. 135, (1988), pp. 303-307). In this method, a complete set of short oligonucleotides or nucleic acid oligomers (probe oligonucleotides), e.g. all 65,536 possible combinations of bases A, T, C, and G of an oligonucleotide octamer, are bound to a support material. The attachment occurs in an ordered grid comprising 65,536 test sites, each rather large amount of an oligonucleotide combination defining one test site, and the position of each individual test site (oligonucleotide combination) being known. On such a hybridization matrix, the oligomer chip, a DNA fragment whose sequence is to be determined (the target) is labeled with fluorescent dye (or ^{32}P) and hybridized under conditions that allow only one specific double-strand formation. In this way, the target DNA fragment binds only to those nucleic acid oligomers (in this example to the octamers) whose complementary sequence corresponds exactly to a portion (an octamer) of its own sequence. Thus, all of the nucleic acid oligomer sequences (octamer sequences) present in the fragment are determined by optical (or autoradiographical) detection of the binding position of the hybridized DNA fragment. Due to the overlapping of neighboring nucleic acid oligomer sequences, the sequential sequence of the DNA fragment can be determined using appropriate mathematical algorithms. One of the advantages of this method lies in the miniaturization of the sequencing and thus in the enormous amount of data that can be simultaneously captured in one operation. In addition, primer and gel-electrophoretic separation of the DNA fragments can be dispensed with. This principle is exemplified in Figure 1 for a 13-base-long DNA fragment (SEQ ID NOS: 2-18).

[CLEAN FORM OF PARAGRAPH 20]

[020] ***Modified Surfaces/Electrodes***

mica	Muscovite lamina, a support material for the application of thin films.
Au-S-$(CH_2)_2$-ss-oligo-spacer-UQ(RC)	Gold film on mica having a covalently applied monolayer of derivatized 12-bp single-strand DNA oligonucleotide (sequence (SEQ. ID. No.: 1): TAGTCGGAAGCA). Here, the oligonucleotide's terminal phosphate group at the 3'-end is esterified with $(HO-(CH_2)_2-S)_2$ to form P-O-$(CH_2)_2$-S-S-$(CH_2)_2$-OH, the S-S bond being homolytically cleaved and producing one Au-S-R bond each. The terminal thymine base at the 5'-end of the oligonucleotide is modified at the C-5 carbon with -CH=CH-CO-NH-CH_2-CH_2-NH_2, this residue, in turn, being joined via its free amino group with the carboxylic-acid group of the modified ubiquinone-50 by amidation. Thereafter, the UQ is reconstituted with the remaining RC.
Au-S-$(CH_2)_2$-ds-oligo-spacer-UQ(RC)	*Au-S-$(CH_2)_2$-ss-oligo-spacer-UQ(RC)* hybridized with the oligonucleotide that is complementary to the ss-oligo (sequence (SEQ. ID. No.: 1): TAGTCGGAAGCA).
Au-S-$(CH_2)_2$-ss-oligo-spacer-Q-ZnBChl	Identical to *Au-S-$(CH_2)_2$-ss-oligo-spacer-UQ(RC)* with the exception that, instead of the RC attached via UQ, Q-ZnBChl is attached as the photoinducibly redox-active moiety.
Au-S-$(CH_2)_2$-ds-oligo-spacer-Q-ZnBChl	*Au-S-$(CH_2)_2$-ss-oligo-spacer-Q-ZnBChl* hybridized with the oligonucleotide that is complementary to the ss-oligo (sequence (SEQ. ID. No.: 1): TAGTCGGAAGCA).

[CLEAN FORM OF PARAGRAPH 96]

[096] Fig. 4 Shows a detailed schematic diagram of the surface hybrid Au-S$(CH_2)_2$-ds-oligo-spacer-Q-ZnBChl of Figure 3 having gold as the solid support material, mercaptoethanol as the spacer (-S-CH_2CH_2- spacer) between the electrode and the oligonucleotide, and -CH_2-CH=CH-CO-NH-CH_2-CH_2-NH- as the spacer between the electron acceptor PQQ and the oligonucleotide, as well as a diagram of the sequence of the photoinduced electron transfer steps. The apoprotein of the RC is indicated only as a shell (solid line) (cf. Structure 1). The 12-bp probe oligonucleotide of the exemplary sequence (SEQ ID NO: 1) 5'-TAGTCGGAAGCA-3' in the hybridized state is shown in detail;

[CLEAN FORM OF PARAGRAPH 98]

[098] Fig. 6 Shows a detailed schematic diagram of the surface hybrid Au-S$(CH_2)_2$-ds-oligo-spacer-Q-ZnBChl of Figure 5 having gold as the solid support material, mercaptoethanol as the spacer (-S-CH_2CH_2- spacer) between the electrode and the oligonucleotide, and -CH_2-CH=CH-CO-NH-CH_2-CH_2-NH- as the spacer between the electron acceptor PQQ and the oligonucleotide, as well as a diagram of the sequence of the photoinduced electron transfer steps. The 12-bp probe oligonucleotide of the exemplary sequence (SEQ ID NO: 1) 5'-TAGTCGGAAGCA-3' in the hybridized state is shown in detail.

[CLEAN FORM OF PARAGRAPH 112]

[112] For incubation, a doubly modified 12-bp single-strand oligonucleotide having the sequence (SEQ ID NO: 1) 5'-TAGTCGGAAGCA-3' was used, which is esterified with (HO-$(CH_2)_2$-$S)_2$ at the phosphate group of the 3'-end to form P-O-$(CH_2)_2$-S-S-$(CH_2)_2$-OH. At the 5'-end, the terminal thymine base of the oligonucleotide is modified at the C-5 carbon with -CH=CH-CO-NH-CH_2-CH_2-NH_2. Approximately 10^{-4} to 10^{-1} molar 2-hydroxy-mercaptoethanol (or another thiol or disulfide linker having a suitable chain length) was added to a $2x10^{-4}$ molar solution of this oligonucleotide in HEPES buffer (0.1 molar in water, pH 7.5 with 0.7 molar addition of TEATFB, see abbreviations) and the gold surface of a test site was completely wetted and incubated for 2-24 hours. During this reaction time, the disulfide spacer P-O-$(CH_2)_2$-S-S-$(CH_2)_2$-OH of the oligonucleotide is homolytically cleaved. In this process, the spacer forms a covalent Au-S bond with Au atoms of the

surface, thus causing a 1:1 coadsorption of the ss-oligonucleotide and the cleaved 2-hydroxy-mercaptoethanol. The free 2-hydroxy-mercaptoethanol that is also present in the incubation solution is likewise coadsorbed by forming an Au-S bond (incubation step).

[CLEAN FORM OF PARAGRAPH 118]

[118] For incubation, a doubly modified 12-bp single-strand oligonucleotide having the sequence (SEQ ID NO: 1) 5'-TAGTCGGAAGCA-3' was used, which is esterified with $(HO-(CH_2)_2-S)_2$ at the phosphate group of the 3'-end to form P-O-$(CH_2)_2$-S-S-$(CH_2)_2$-OH. At the 5'-end, the terminal thymine base of the oligonucleotide is modified at the C-5 carbon with -CH=CH-CO-NH-CH_2-CH_2-NH_2. A $2x10^{-4}$ molar solution of this oligonucleotide in the hybridization buffer (10 mM Tris, 1 mM EDTA, pH 7.5 with 0.7 molar addition of TEATFB, see abbreviations) was hybridized with a $2x10^{-4}$ molar solution of the (unmodified) complementary strand in the hybridization buffer at room temperature for approx. 2 hours (hybridization step). After hybridization, approx. 10^{-4} to 10^{-1} molar 2-hydroxy-mercaptoethanol (or another thiol or disulfide linker having a suitable chain length) was added to the now $1x10^{-4}$ molar double-strand oligonucleotide solution and the gold surface of a test site was completely wetted and incubated for 2 - 24 hours. During this reaction time, the disulfide spacer P-O-$(CH_2)_2$-S-S-$(CH_2)_2$-OH of the oligonucleotide is homolytically cleaved. In this process, the spacer forms a covalent Au-S bond with Au atoms of the surface, thus causing a 1:1 coadsorption of the ds-oligonucleotide and the cleaved 2-hydroxy-mercaptoethanol. The free 2-hydroxy-mercaptoethanol that is also present in the incubation solution is likewise coadsorbed by forming an Au-S bond (incubation step).